REMARKS

Claims 1-157 are in this case. Claims 4-16, 24, 27, 31-40, 43-58, 61, 63, 65, 67, 69, 70, 75-80, 87-89, 93, 96-139 and 156 have been withdrawn from consideration as directed to a non-elected invention. This response amends claims 1, 19, 81, 82, 91, 144, 147 and 148.

Information Disclosure Statement

The Office Action indicates that no copies of references were provided in the information disclosure statement (IDS) filed October 10, 2002. The undersigned encloses herewith a copy of the post card receipt of the filing of that IDS indicating receipt at the U.S. Patent Office of 101 references. Applicants have thus complied with the requirements of 37 CFR 1.98(a)(2) and all of the references listed on the IDS filed should be considered by the Examiner. Replacement of all of the references represents a significant effort and cost. The undersigned will be happy to provide a second copy of references to the Examiner, if necessary. The undersigned notes that it appears that all of the references from this IDS are available to the Examiner on the PAIR system. The undersigned would appreciate an initialed 1449 form indicating receipt of all copies of references cited.

Objection to the Specification

In the response filed March 4, 2004, Applicant amended the specification to add material from a reference that had been incorporated by reference in the specification. The undersigned attorney prepared the original application as well as the amendment and declares that the material added to the specification in the amendment filed March 4, 2004 consists of the same material incorporated by reference from Ranaschi et al.

It is believed that the declaration made herein above is sufficient to meet the requirements of proper incorporation by reference. It is believed that the attorney of record can provide such a declaration within the body of a response

and that a separate paper is not required. If this is incorrect, the undersigned requests a telephone call from the Examiner to request the filing of a separate paper. In view of this declaration, the new matter rejection related to the amendment of the specification and with respect to claim 152 should be withdrawn.

Claim Amendments

Claims 1, 19, 81, 82, 91, 144, 147 and 148 have been amended as suggested by the Examiner to improve their clarity by correcting grammar, adding definitions of FE, RE and SRE variables and correcting obvious typogrpahic errors. The amendments are fully supported by the claims as filed and by the specification as a whole. No new matter is added.

Claim Objections

Claim 81 is objected to for use of the term ROMP. Claim 81 has been amended to add ring-opening metathesis polymerization.

Claim 147 is objected to for being of improper dependent form. An obvious typographic error in this claim has been corrected so that the claim now depends from claim 146.

Claims 156 and 157 were objected to because in the amendment of the claims the status of claims 156 and 157 as newly added was not properly listed. These claims are included in the current listing of claims as "previously presented." It is believed that this clarification is all that is necessary. If any other action is required, the undersigned requests a telephone call from the Examiner to indicate what is needed.

In view of the amendments to the claims and the clarification of status given, it is believed that all the claim objections should be obviated.

The Rejections

Rejections under 35 USC §112, second paragraph

Claims 1-3, 17-23, 28-30, 41, 42, 59, 60, 62, 64, 66, 68, 71-74, 81-86, 90-92, 94-95, 140-146 and 148-155 and 157 are rejected as being indefinite. Applicant has amended claims 1, 19, 82 and 91 which is believed to obviate this rejection. Applicant traverses the rejection of claims 83-86, 90, 91, 92, 94, 95, 144, 148, 149 and 150 in view of the amendment of claims 82 and 91.

Claim 1 has been amended to clarify that the signal recognition element is bonded to the molecular scaffold.

Claim 19 has been amended to depend from claim 17 which is believed to render the claim definite.

Claim 82 has been amended to remove the quotation marks around the term BB. It is noted that each compound of the listed formula can contain BB units. The claim has been amended to clarify that each of the BB units in the chemical formula given can be the same or different. The recitation of "in a block or random arrangement" has been deleted as unnecessary.

The terms "FE," RE" and "SRE" in claim 82 are not intended to be abbreviations but are used as variables in the chemical formula given. These variables are now clearly defined in claim 82.

Similar amendments have been made in claim 91.

The variables FE, RE and SRE have been retained in all of claims 83-86, 90, 91, 92, 94, 95, 144, 148, 149 and 150. The variables are properly defined in claims 82 and 91 from which these claims depend and it is believed to be unnecessary and redundant to define the variables in each dependent claim.

In view of the foregoing, all of the rejections under 35 USC §112 second paragraph are believed to be obviated.

Prior Art Rejections

Claims 151-155 and 157 were said to be rejected under 35 U.S.C. § 112, second paragraph, but no reason for their rejection was given. Applicants submit that this rejection is improper.

Claims 1, 81, 82, 83, 85, 86, and 90 are rejected under 35 U.S.C. §102(a) as being anticipated by Gordon et al., (Chemistry 8 Biology 2000, vol. 7:9-16). Applicants respectfully traverse this rejection.

The Office Action states:

> Claims 1, 81, 82, 83, 85, 86, and 90 are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal recognition elements are bonded to molecular scaffold; wherein the multivalent ligand has the general formula of claim 82, and has functional groups that act as markers.
>
> Gordon throughout the publication and at the abstract, p. 9, para 4-p. 10, para 2, teaches, teaches using ring-opening metathesis polymerization (ROMP) to generate to form multivalent arrays that include multivalent ligands for binding to cell surface receptors, e.g. through epidermal growth factor; teaches at Figures 3-5, polymers of the general formula of claims 82 and 91, at p. 13, para 2 and 3, teaches multivalent ligands coupled to a fluorescent reporter group that is fluoresce in, where the signal recognition element binds to L-selectin, which acts to recruit white cells to sites of tissue damage, and so acts as a guide to cells, i.e., chemoattractant, as demonstrated on human T-cells (Jurkat cells).

Applicants disagree with the characterization of the Gordon reference in that Gordon while teaching that certain multivalent ligands bind to L-selectin,

does not demonstrate that this binding effects any biological response. Gordon does not show that binding of a multivalent ligand to L-selecting "recuits white cells to sites of tissue damage." The Gordon reference provides very useful methods of synthesis for the preparation of multivalent ligands. The Gordon reference employs ligand binding with a fluorescent reporter to visualize cells and suggests on page 14, column 1, lines 3-5 that the ligands produced using the methods disclosed "will facilitate a wide range of mechanistic investigation of cell surface-ligand binding events." Thus, the Gorodon reference suggests that the multivalent ligands disclosed should be used to investigate biological effects. The rejected claims are all directed to methods of inducing a biological response. Since Gordon does not demonstrate induction of such a response, it does not provide all of the elements of the claims and as such does not anticipate the claims. This rejection should be withdrawn.

Further, with respect to the rejection of claims 83, 85 and 86 over the Gordon reference, Gordon does not teach any multivalent ligand which comprises a peptide (as in claims 83), a chemoattractant (as in claim 85) or an epitope (as in claim 86).

Each of claims 83, 85 and 86 should be considered patentable over the Gordon reference.

Claims 1-3, 17, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 140, 142, 143, 151, 154, 155, 157 are rejected under 35 U.S.C. § 102(b) as being anticipated by Whitesides et al., WO 98/46270. Applicants respectfully traverse this rejection.

The Office Action States:

> Claims 1-3, 17, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 140, 142, 143, 151, 154, 155, 157 are drawn to methods for inducing a biological response in a biological system comprising

one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal recognition elements are bonded.

Whitesides, throughout the publication and at p. 3, lines 11-24, p. 7, lines 24-31, p. 14, lines 1-9, p. 15, lines 20-31, teaches multivalent ligands on a polymeric backbone of the form Y-(A)„where Y is a framework, A is a functional group, and n is an integer greater than 10, 50 or more, or about 100 or more and wherein the functional group that is a signal recognition is covalently bonded to the framework that is a molecular scaffold, such as a liposome; teaches at p. 32, lines 7-13, polyvalent presenters that include Sialyl Le" that bind leukocyte receptor sites including integrins and selectins and are elements involved in signal recognition, inducing intracellular and intercellular responses; teaches at p. 60, line 26-p.61, line 20 modulation of cell-cell interactions by polyvalent presenters, (which include multivalent ligands), whereby numerous cell-cell interactions can be promoted or inhibited, such as neutrophil attachment to endothelial cells during inflammation; teaches at Table 2, p. 62, line 4-p. 63, line 7, cell-cell interactions that include neutrophil, endothelial cells, T – cells, and the release of platelet granules; teaches at p. 87, lines 3-18, teaches cytokine production by replacing a stimulator cell in a cell-cell interaction that normally leads to cytokine secretion, e.g., the L-selectin ligands to simulate monocytes and macrophages to produce tumor necrosis factor; teaches at p. 96, line 1-p. 99 line 16, in vitro assays; at p. 97, line 31- p. 99, line 16, teaches cross-linking multivalent receptors on the cell by agglutinins to prevent the biological response of viral binding to the cell surface.

Again Applicants disagree with the characterization of the Whitesides reference. Whitesides et al. do teach the synthesis of certain multivalent ligands and do teach binding of such ligands. However, although there is much discussion in the reference, as noted by the Examiner above, concerning biological responses, the Whitesides et al. reference does not demonstrate induction of a biological response. Whitesides et al. demonstrate binding by ligands and inhibition of binding. In Example 1, inhibition of absorption of influenza virus to erythrocytes (page 118, lines 19-20). In Example 2, inhibition of platelet aggregation is assayed. In Example 3, prevention of adhesion of ricins to erythrocytes is assayed (page 125, lines28-29). In Example 4 (see page 140,

lines 14-20) inhibition of sperm-egg binding is assayed. The Office Action characterizes "viral-binding" as a biological response. Applicants disagree with this characterization. Viral-binding is a binding event not a biological response. The Whitesides et al. reference does not demonstrate any example of "induction of a biological response" by a multivalent ligand and does not provide any enabling teaching of such induction. Thus, this reference does not teach all of the elements of Applicants' claimed invention and should not be considered to anticipate these claims. This rejection should be withdrawn with respect to all of the claims.

With respect to claims 20-23 or 30, Whitesides et al. do not teach a multivalent ligand that functions to induce a biological response in any of an epithelial cell, an endothelial cell, a cell of the immune system, a lymphocyte, a leukocyte, a neutrophil, a B-cell or a T-cell. This rejection should be withdrawn with respect to these claims.

With respect to claims 28, 29, 151, 154 and 155 Whitesides et al. do not teach a multivalent ligand that functions for the initiation or release of an intracellular signal by a cell. Further with respect to claim 155, Whitesides et al. do not teach a multivalent ligand that releases a chemical signal which is a naturally-occurring drug, a hormone, an antigen, a growth factor, a cytokine, a protein, a peptide, a derivatized peptide, a saccharides, a derivatized saccharide, a nucleic acid, a cell nutrient, or an epitope.

With respect to claims 41 and 42, Whitesides et al. do not teach a multivalent ligand that functions to reorganizes receptors on the surface of a cell to modulate a biological response.

With respect to claim 140, the Office Action does not point to any specific passage in the Whitesides et al. reference that teaches the use of a multivalent

ligand bound to a solid support. Whitesides et al., thus, do not appear to teach a multivalent ligand that is bonded to a support.

All of claims 28, 29, 151, 154, 155, 41, 42 and 140 should, thus, be considered to not be anticipated by the cited reference. This rejection should be withdrawn with respect to these claims.

Claims 1, 81, 82, 83, 85, and 90 are rejected under 35 U.S.C. §102(e) as being anticipated by Kiessling et al., US 6,291,6162. Applicants respectfully traverse this rejection.

The Office Action states:

> Claims 1, 81, 82, 83, 85, and 90 are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal recognition elements are bonded to molecular scaffold; wherein the multivalent ligand has the general formula of claim 82, and has functional groups that act as markers.
>
> Kiessling et al., US 6,291,616, at col. 1, lines 10-48, teaches using ring-opening metathesis polymerization (ROMP) to generate to form multivalent arrays that include multivalent ligands for binding to cell surface receptors, e.g. through epidermal growth factor, resulting in dimerization of the transmembrane receptor; teaches at col. 10, line 32-col. 11, line 46, polymers of the general formula of claims 82 and 91, col. 13, line 44- col. 14, line 32, teaches multivalent ligands coupled to a fluorescent reporter group that is fluorescein, where the signal recognition element binds to L-selectin, which acts to recruit white cells to sites of tissue damage, and so acts as a guide to cells, i.e., chemoattractant, as demonstrated on human T-cells (Jurkat cells).

Applicants disagree with the characterization of US 6,291,616. This patents teaches "methods of preparing a telechelic polymer (mono- or bi-telechelic) that use a ruthenium or osmium carbene catalyst and a capping agent, at least one of which is functionalized" (See Abstract). There is no

demonstration in this reference that any multivalent ligand induces a biological response as required by Applicants' claims herein. Thus, the cited art does not teach Applicants' claimed method and as such cannot be found to anticipate Applicants' claims. This rejection should be withdrawn.

Claims 1, 2, 17, 18 and 19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Whitesides et al., WO 98/46270 and Shea et al., Biophysical Journal, 1997, vol. 73, pp. 2949-2959. Applicants respectfully traverse this rejection.

The Office Action states:

> Claims 1, 2, 17, 18 and 19 are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal recognition elements are bonded to molecular scaffold, wherein the multivalent ligand modulates signal transduction mediated by G-protein coupled receptors.

The characterization of Whitesides et al. is noted above.

The Office Action continues:

> Whitesides et al. does not teach G protein coupled receptors.
>
> Shea et al., teach the G-protein activation and formation of cross-linked receptors by multivalent ligands. Shea, at the abstract, and p. 2949, para 1, teaches the initiation the cascade of signal transduction by multivalent ligand binding to G-protein coupled receptors in the plasma membrane, which acts as a first step.

The Office Action alleges that:

> It would have prima facie obvious for one of ordinary skill in the art at the time of the invention to combine methods for inducing biological response by multivalent ligands with multivalent ligands that modulate signal transduction mediated by G-protein coupled receptors.

> One of ordinary skill in the art would have been motivated to use multivalent ligands that modulate signal transduction mediated by G-protein coupled receptors, in order to initiate a biological response that is a cascade of signal transduction, as taught by Shea et al.

The deficiencies of the Whiteside et al. reference at noted about. Whitesides et al. does not teach induction of any biological response by a multivalent ligand. Shea et al. appears to relate to kinetic modeling of ligand binding in G-protein activation. Shea et al. does not demonstrate the induction of a biological response by a multivalent ligand in any biological system. Thus, the Shea et al. reference does not cure the deficiency of the Whitesides et al. reference and the combination of these two references does not teach or suggest Applicants' methods as claimed. This rejection should be withdrawn.

Claims 1, 62, 64, 66, 82, 83, and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO 98/46270, Kiessling et al., US 6,291,616, and Painter et al., Journal of Cell Biology, 1987, vol. 105, pp. 2959-2971. Applicants respectfully traverse this rejection.

The Office Action states:

> Claims 1, 62, 64, 66, 82, 83, and 84 are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal recognition elements are bonded to molecular scaffold, and wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide.

The characterization of Whitesides et al. and Kiessling et al. are noted above.

The Office Action alleges:

> Neither of Whitesides et al. or Kiessling et al. do teach a derivatized peptide that is an N-formylated peptide, US 6,291,616, teach methods for inducing a biological response by multivalent

ligands, wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide.

Painter et al. teach a derivatized peptide that is an N-formylated peptide that is a ligand that binds to a glycoprotein receptor and acts as a recognition element to stimulate chemotaxis of human neutrophils.

The Office Action alleges that:

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to combine methods of inducing biological response by multivalent ligands that bind to receptors, with derivatized or N-formylated peptides.

The deficiencies of the Whitesides et al. and Kiessling et al. references are noted above. Neither of these references teaches the induction of a biological response by a multivalent ligand. Painter et al. does not cure these deficiencies. Painter et al. does not appear to teach anything about a multivalent ligand. There is no teaching or suggestion in any of Whitesides et al. or Kiessling et al., alone or in combination, that a multivalent ligand carrying an N-formylated peptide would induce a biological signal. More specifically, there is no teaching or suggestion that a multivalent ROMP ligand carrying N-formylated peptides would induce a biological effect. This rejection should be withdrawn.

Allowable Claims

Claims 91, 92, 94 and 95 were not rejected over the prior art cited. These claims were rejected under 35 U.S.C. § 112, second paragraph. The amendment of claim 91 is believed to obviate this rejection for all of these claims. It is believed that claims 91, 92, 94 and 95, at least, are allowable and passage to issuance is respectfully requested.

Claims 141, 144, 145, 146, 147, 148, 149 and 150 were not rejected over the prior art cited. Claim 147 was objected to for improper antecedent basis and has been amended to depend from claim 146. The amendment of claim 141 is believed to obviate the rejection of this claim and claims 144, 145, 146, 148 -150

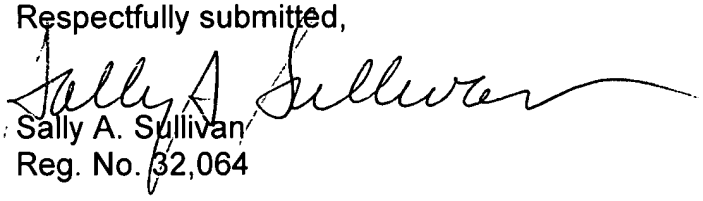
under 35 U.S.C. § 112, second paragraph. It is believed that all of claims 141, 144-150, at least, are allowable and passage to issue is respectfully requested.

Claims 152 and 153 were not rejected over the prior art cited. These claims were said to be rejected under 35 U.S.C. § 112, second paragraph, but no reason for this rejection was given. It is thus believed that claims 152 and 153 are allowable and passage to issue is respectfully requested.

Conclusion

In view of the amendments and arguments presented, the claims herein should be considered in condition for allowance and passage to issuance is respectfully requested. This response is accompanied by a Petition for Extension of Time of three months with required fee. No excess claims fees are believed due. A check in the amount of $490 accompanies this filing. If the amount submitted is incorrect, please charge any deficiency or credit any overpayment to deposit account 07-1969.

Respectfully submitted,



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